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ONE HUNDRED FIFTH CONGRESS

Congress of the United States

House of Representatives

COMMITTEE ON GOVERNMENT REFORM AND OVERSIGHT

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May 22, 1998

Harold Varmus, Director
National Institutes of Health
9000 Rockville Pike
Bethesda, MD 20892

Steven E. Hyman, Director
National Institute of Mental Health
Parklawn Building - 5600 Fishers Lane
Rockville, MD 20857

Dear Drs. Varmus and Hyman:

The Committee on Government Reform and Oversight, has conducted a series of oversight hearings focusing on patient access to medical treatment. During a hearing held April 22, 1998 we heard testimony concerning the ethical treatment of human subjects of clinical research. Pursuant to media reports of fenfluramine use in non-therapeutic scientific research on economically disadvantaged children, questions were posed to FDA Lead Deputy Commissioner Michael A. Friedman about FDA's role in allowing the use of fenfluramine in research in children after it was banned for use in medical treatment of adults.

It is the Committee's understanding that the NIH, through the NIMH, played an important role in the approval and regulation of the fenfluramine research that took place within the New York Psychiatric Institute via the Columbia and the Queens College Projects. Thus, pursuant to its authority under Rules X and XI of the House of Representatives and the oversight responsibilities of Committee on Government Reform and Oversight, we request the following records and information.

- I. For both the Columbia and Queens College projects please provide:
- A. A complete copy of the Research Applications
B. A complete copy of the in-house NIMH evaluations
C. A list of all members of the external (outside NIMH) review committee and a complete copy of any written comments or memoranda from the committee.

- D. A complete copy of the NIMH approval statement
 - E. A list of all members of the IRB and its comments and approval statement
 - F. A complete copy of the informed consent form or forms used in the above mentioned projects
 - G. All additional printed information provided to family members as a part of obtaining their consent
 - H. All NIH and NIMH memoranda relating to these projects
 - I. The name of NIMH officers responsible for each project
- II. For the Queens Project:
- A. A breakdown of the racial composition of the research subjects
- III. For the Columbia Project:
- A. All NIMH memoranda concerning the method of obtaining subjects through the department of probation
 - B. All project communications, memoranda, etc. concerning the method of obtaining subjects through the department of probation
- VI. Please provide written responses to the following:
- A. In general, normal, healthy children are not supposed to be subjected to non-therapeutic potentially dangerous experimental research . Why was the research in both projects allowed in light of this?
 - B. What consideration did NIMH give to the implication of the Columbia project focus on impoverished non-white children?
 - C. At the time both projects were begun, there was already research indicating that fenfluramine can cause severe and sometimes permanent impairment in serotonin nerve cells at therapeutic doses in animals. Why was this research ignored or how was it excused? Was this research made part of the informed consent form, and if not, why not?
 - D. At the time both projects were begun, there was already international concern about reports of cardiac valve injury from fenfluramine. Was this taken into consideration, and if so, why was the research allowed? Was this made a part of the informed consent requirement, and if not, why not?

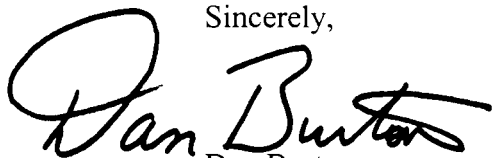
- E. At the time that evidence mounted concerning the neurotoxic and cardiotoxic effects of fenfluramine, why did NIMH not intervene to stop these studies?
- F. Once fenfluramine was withdrawn from the market, why did NIMH not take immediate steps to make sure that all fenfluramine research on children and adults be stopped?
- G. The hypotheses involved in the fenfluramine studies of both projects were highly speculative. What, if any, consistent body of research in animals or in adults justified the extension of this research into children?
- H. In 1994, after criticism of projects exactly like those involving fenfluramine, the National Institutes of Health convened a panel on "NIH Research on Anti-social, Aggressive and Violence-related Behaviors and Their Consequences." This panel made serious criticism of biologically oriented research focusing on individuals in regard to large social issues such as crime and delinquency as well as race.
 - 1. What new measures did NIMH take to review and monitor projects such as the fenfluramine research following these criticisms?
 - 2. What measures has NIMH taken to correct the imbalance toward biological and individual research in contrast to more socially oriented research?
- I. What changes are necessary at NIMH to prevent future such experimentation on normal as well as diagnosed children?
- J. What measures were taken to monitor adverse effects of fenfluramine on these children? Provide copies of the specific check lists and questionnaires were used? How were the parents involved in evaluating potential adverse effects?
- K. Why did the published papers not discuss adverse effects?
- L. What long-term follow up tests (one day, one week, one month and one year after) were developed and conducted to test for potential adverse effects?
- M. The Committee has been informed that during these tests the children, who were as young as age six, were subjected to a twelve-hour fast, followed by nothing by mouth for five or more hours while being subjected to intravenous catheterization in an experimental setting. What adverse psychological effects could be anticipated in such young children from this kind of treatment?

- N. What efforts were made to help these children to understand and to recover from any post-traumatic effects from this research?
- O. Who was present during the actual experiment? Were any of those present trained in child psychology and prepared to help the children with their fears?
- P. Were the parents in the experimental room throughout the procedures? If not, what are the implications of subjecting children as young as six to isolation from their parents during an experimental and potentially uncomfortable and frightening procedure?
- Q. What are the implications of off-label use of potentially dangerous drugs in children?
- R. What are the implications of giving children drugs that have not been approved for use in children? How can there be any certainty that the drugs will not prove especially harmful to children when they have not been tested and FDA-approved for children?
- S. Why didn't NIMH require a new round of IRB review for the use of fenfluramine in experimental research in children when the drug was withdrawn from the market?
- T. Single dose studies of fenfluramine in adults have shown major side effects (including relative disability) at doses of 1mg/kg [Muldoon, M.F.; Manuck, S.B.; Jansma, C.L.; Moor, A.L.; Perel, J.; and Mann, J.J. (1996) D, L-fenfluramine challenge test: Experience in nonpatient sample. *Biological Psychiatry* 39, 761-768]. Why did NIMH approve the use of a dose in children that was known to cause such serious adverse effects in adults?
- U. The Columbia study reports in its publication that they used a dose of 10mg/kg of fenfluramine. Although they never published a correction, Columbia reportedly claims this was a misprint and that the dose was actually 1mg/kg. Has NIMH audited the study to determine the actual dose used? If 10mg/kg was used, should it have been allowed in experiments on children, and how did NIMH justify approval of this dangerous study?

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Thank you for your prompt attention to this request. Please provide the requested information no later than the close of business, June 10, 1998. If you have any questions regarding this request, please contact Committee Counsel Laurie S. Taylor at (202) 225-5074.

Sincerely,

A handwritten signature in black ink that reads "Dan Burton". The signature is fluid and cursive, with the first name "Dan" and last name "Burton" clearly distinguishable.

Dan Burton
Chairman

cc: The Honorable Chris Shays